Review

Recent developments in biologic therapies for the treatment of patients with systemic lupus erythematosus

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Abstract

SLE has a complex pathogenesis, and multiple therapeutic targets have been discovered in recent years. In spite of belimumab being approved by the US Food and Drug Administration and the widespread use of rituximab, there have been many failed attempts to treat SLE successfully using biologic agents. In this review, we consider newer biologic approaches that might offer the hope of improving the outcome of SLE patients. These include the fully humanized anti-CD20 mAbs, PEGylated anti-CD40L, IFN α inhibitors, rigerimod and immune complexes blockade.

Key words: lupus, biologic, anti-CD20, anti-CD40L, dapirolizumab, ofatumumab, obinutuzumab, rigerimod, interferon, FC γ R

Rheumatology key messages

- There is still considerable morbidity with conventional immunosuppression in SLE patients.
- Successful biologic use in SLE is a decade behind that for rheumatoid and psoriatic arthritis.
- A number of new promising biologic therapies for SLE are in clinical trials.

Introduction

The use of biologic therapies in the treatment of patients with SLE is, arguably, at least a decade behind their use in RA, PsA and AS. The need for more successful biologic or other new therapies remains important as it is clear we have reached the limit of what can be achieved with conventional immunosuppression [1]. SLE patients have ~90% survival rate at 10 years [2] with considerable morbidity, which remains very unsatisfactory for a disease that often develops before age 30.

Some encouragement is taken from the approval of belimumab by the US Food and Drug Administration (and more recently the National Institute for Health and Clinical Excellence) and the widespread use of rituximab (in spite of two trials that did not meet their endpoints). Neither drug alone will be a panacea for SLE, although

interestingly attempts to combine those drugs are now being pursued. In this mini-review we will focus on several new or modified approaches that we believe offer the best hope of improving the outcome of SLE patients. Our choice of new approaches is subjective, based on our reading of the recent literature.

Pathogenesis

The pathogenesis of SLE involves genetic and epigenetic factors, environmental triggers and immunological abnormalities. These abnormalities include defective apoptosis and loss of tolerance; inadequate development of dendritic cells; defective function of regulatory T cells and B cells; defective B and T cells apoptosis and defective signalling pathways. Fig. 1 shows the link between these factors and the sites of action of relevant therapeutic agents.

CD20 blockade

B cells play an essential role in the development of SLE. Blocking B cells with rituximab, a chimeric mAb against antigen CD20, is well established in SLE. Because it is a chimeric antibody, can cause allergic responses in ~10% of SLE patients. Fully humanized mAbs anti-CD20 have been developed including ofatumumab and obinutuzumab.

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Fig. 1 Simplified diagram of SLE pathogenesis and site of action of therapeutic agents

Defective apoptosis results in production of uncleared nuclear material leading to dendritic-cells (DC) activation and BCR stimulation. DC will produce a number of cytokines, which will result in B-cell activation (BAFF and APRIL) but also differentiation of monocytes to macrophages (IFN α) that will present self-antigens to T and B cells but also produce cytokines. The activation of B cells needs a co-stimulatory signal between T-cell receptor (TCR) and MHC in antigen presenting cells (APC) but also CD40: CD40L binding with macrophage and dendritic cells. B-cells activation, differentiation, and proliferation leads to autoantibody production. Immune complex formation and tissue deposition results in organ damage. pDC: plasmacytoid dendritic cells; mDC: myeloid dendritic cells; fDC: follicular dendritic cells; BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; BAFF: B cell activating factor; APRIL: a proliferation inducing ligand; APC: antigen presenting cells.

Ofatumumab is a mAb IgG1 anti-CD20 approved for chronic lymphocytic leukaemia. Experience of its use in SLE is restricted to a small number of cases. For example, an SLE patient whose previous flares had responded to rituximab, but became allergic to it, received three infusions of ofatumumab and achieved an SLEDAI decrease from 15 to 2, a reduction of anti-dsDNA antibodies levels >90% and C3 normalization [3]. An SLE patient with autoimmune haemolytic anaemia refractory to rituximab, achieved B-cell depletion after ofatumumab, with remission of autoimmune haemolytic anaemia and a SLEDAI of 0 [4]. Four patients with LN achieved proteinuria and anti-dsDNA reduction after ofatumumab [5]. Formal clinical trials in SLE are awaited.

Obinutuzumab, a glycol-engineered mAb anti-CD20, is being used in the treatment of non-Hodgkin's lymphoma. An *in vitro* study comparing rituximab to obinutuzumab in SLE demonstrated the latter to be a more efficient B-cell depletor [6]. A 52-week, phase II trial studying safety and

efficacy in LN is currently recruiting (NCT02550652). Its primary outcome is complete renal response.

B-cell intracellular signalling blockade—Bruton's tyrosine kinase

Bruton's tyrosine kinase (BTK) is a component of B-cell receptor signalling, involved in regulating cell proliferation and survival. Its blockade results in B-cell apoptosis. B-cells overexpressing BTK in mice led to anti-dsDNA antibody production and SLE-resembling organ involvement. Many inhibitors of BTK are in development, including ibrutinib and GDC-0853.

Ibrutinib is a tyrosine kinase selective and irreversible inhibitor. It binds to BTK causing B-cell apoptosis. Pre-clinical trials showed ibrutinib reduced levels of autoantibodies (anti-nucleosome, anti-histone and anti-ssDNA but not anti-dsDNA) and renal disease [7]. However, no current clinical trial is ongoing in SLE.

GDC-0853 is another BTK inhibitor [8]. A phase II trial in SLE is ongoing (NCT02908100), to evaluate the safety and efficacy in patients with moderate-to-severely active SLE.

T cell co-stimulation blockade

B-cell immune stimulation follows interaction with T cells and antigen-presenting cells via co-stimulatory signals, notably CD40/40L, CD28, cytotoxic T-lymphocyte antigen 4, and CD80/CD86.

Rigimerod is a 21-mer linear peptide derived from the small nuclear RNP U1-70K, whose mechanism of action seems to be due to chaperone-mediated autophagy [9]. By reducing the stability of MHC molecules that present antigens to T cells, it blocks antigen presentation to autoreactive T cells, which in turn blocks B-cells maturation.

A phase II trial involved 20 patients with moderately active SLE who received three s.c. injections. Significant improvement in the SLEDAI score was reported with the 200 µg/dose [10]. A phase IIb trial showed a significant reduction of disease activity [11]. One hundred and forty-nine patients were randomized to receive rigimerod or a placebo every 2 or 4 weeks. Patients with SLEDAI-2K ≥ 6 who received rigimerod 200 µg every 4 weeks achieved a statistically higher Systemic Lupus Erythematosus Responder Index (SRI)-4 response at week 12 (67.6 vs 41.5%, $P < 0.025$) and week 24 (84.2 vs 45.8%, $P < 0.025$). A phase III trial is underway, whose primary outcome is SLEDAI-2K reduction ≥ 4 (NCT02504645).

CD40 ligand (CD40L) is a protein expressed on activated T cells and a member of the TNF family. Its binding to CD40 on antigen-presenting cells and B cells induces co-stimulation and promotes B-cell maturation. Anti-CD40L mAbs block co-stimulation in experimental models. A phase II trial in 28 patients with proliferative LN showed significant reduction in circulating levels of anti-dsDNA antibodies and increased C3 levels, but was associated with thromboembolic events [12]. Another phase II trial of a different anti-CD40L mAb had no major adverse events (AE), however, efficacy was not proven [13]. The thromboembolic events were evidently caused by the functional Fc region of anti-CD40L, which triggers platelet aggregation by interacting with platelet Fc γ RIIA receptor. In dapirolizumab the Fc portion has been changed to a high molecular polyethylene glycol without loss of efficacy [14]. A 32-week, phase IB trial showed safety and tolerability of intravenous dapirolizumab in SLE patients. Clinical response was evident by both SRI and BILAG-based Combined Lupus Assessment (BICLA) assessments [15]. A 24-week phase II trial, followed by observational period to evaluate efficacy and safety on moderately to severely active SLE is recruiting (NCT02804763). The primary outcome is the BICLA response rate at 24 weeks.

Interferon blockade

IFNs are a family of glycoproteins that consist of type I IFN (IFN-I) (including 12 isoforms of IFN α and one of IFN β) and type II IFN (includes only IFN γ). IFN-I binds to the type I

IFN receptor (IFNR), IFN γ binds to another receptor. IFN activates multiple signalling pathways, especially Janus kinase. IFN dysregulated activity and signalling is associated with autoimmune disease development. Rarely, when IFN α has been used, for example, in hepatitis C and cryoglobulinaemic vasculitis, autoimmune conditions, including SLE, have been reported to develop [16, 17]. IFN-I levels are higher in SLE and recent studies have shown a link between IFN α levels and disease activity. In *Ifnar1* gene knockout mice, reduced disease activity is seen.

Rontalizumab is a humanized IgG1 mAb against IFN α . A phase I trial proved safe but showed no clinical benefit in those with a high IFN signature [18]. A phase II trial evaluated efficacy and safety of rontalizumab in 159 patients with moderate to severe SLE. Patients were randomized to receive rontalizumab 750 mg or placebo every 4 weeks plus standard of care (SOC) (part 1) and subsequently, 300 mg rontalizumab or placebo every 2 weeks (part 2). The results did not confirm rontalizumab's general superiority, however paradoxically, in the low IFN signature group SRI response rates were superior in 31% ($P = 0.0285$) and the SELENA-SLEDAI flare index rate was reduced [19]. However, no further trial is ongoing.

Sifalimumab is a fully human IgG1 κ mAb that binds to most subtypes of IFN α and neutralizes it. Two phase I trials showed safety and IFN signature reduction in a dose-dependent manner. A 52-week phase IIb trial followed by a 22-week safety follow-up, enrolled 431 patients randomized to receive placebo or sifalimumab (200, 600 or 1200 mg) every 28 days in addition to SOC. In all sifalimumab groups, the response rates were significantly higher than in the placebo group, however, only the group with the high IFN signature patients achieved significant improvement in SRI-4. Cutaneous Lupus Erythematosus Disease area and Severity Index (CLASI) as well as joint counts showed significant improvement. No differences in lowering anti-dsDNA antibodies or normalizing C3/C4 levels were observed. Herpes zoster was the principal AE as expected by IFN suppression [20]. Currently no phase III trial is ongoing.

Unlike the other IFN blockers, directed against IFN, anifrolumab is a fully human IgG1 κ mAb that blocks subunit 1 of the IFNR and consequently both IFN α and IFN β . A phase I trial showed safety and sustained IFN signature reduction in SSc patients. In a 52-week phase IIb lupus trial, 305 patients were randomized to receive placebo, anifrolumab 300 mg or 1000 mg every 4 weeks until week 48 as well as SOC [21]. Active LN or neuropsychiatric SLE were excluded. The primary efficacy end point was a combination of the SR-4 at weeks 24 and 52 with a sustained reduction in oral corticosteroids from weeks 12 to 24. At both weeks 24 and 52, the response was achieved in a significantly higher number of patients receiving both dosages of anifrolumab (300 mg, $P = 0.014$ and 1000 mg, $P = 0.063$). When evaluating the sub-groups by IFN signature levels, those with high levels of IFN achieved significantly better results compared with placebo at both 24 and 52 weeks. Significant

TABLE 1 Biologics used in SLE, mechanism of action, targeted receptors and main trials

Biologic	Immunologic action	Evidence to date in SLE	Number of patients	Inclusion criteria	Primary outcome	Therapeutic regime	Results	Future trials in SLE	Inclusion criteria	Primary outcome	Therapeutic regime	Prospects
Oritumumab	B-cell depletion	Case reports [3–5]	1, 1 and a series of four patients	-	-	Variable	Reduction on disease activity/Anti-dsDNA reduction and C3 normalization	No trials ongoing	-	-	-	Promising, needs clinical studies
Obinutuzumab	B-cell depletion	Pre-clinical [6]	-	-	-	-	B-cell depletion 2-fold the rituximab	Phase II ongoing on LN	Class III or IV LN	Complete Renal Response at week 52	1000 mg on days 1, 15, 168 and 182 plus MMF	Promising, awaits clinical results
Ibrutinib	BTK inhibition	Pre-clinical [7]	-	-	-	-	BTK inhibition on mature B-cell and APC	No trials ongoing	-	-	-	Promising, needs clinical studies
GDC-0853	BTK inhibition	Pre-clinical and phase I [8]	111	-	-	20, 60, 150 and 250 mg BID, and 500 mg QD	BTK inhibition on mature B-cells	Phase II ongoing	Moderate to severe SLE	SRI-4 response	Low and high dose daily vs placebo	Promising, awaits results
Rigirimod	T-cell blockade	Phase IIb [10, 11]	149	ITT SLEDAI ≥ 6 No BILAG A	SRI-4	200 μ g every 2 or 4 weeks	Improvement in subpopulation SLEDAI ≥ 6 . Best results 200 μ g every 4 weeks	Phase III ongoing	SLEDAI-2K ≥ 6 points	SRI-4 response	200 mcg every 4 weeks	Very promising, awaits results
Dapirolizumab	T-cell co-stimulation blockade	Phase Ib [15]	24	SELENA-SLEDAI ≥ 4	SRI-4 and BICLA	First dose 30 mg/kg then five doses of 15 mg/kg every 2 weeks	SRI-4 and BICLA response across several endpoints	Phase II ongoing	Moderate to severe disease activity	BICLA response rate at week 24	Three different doses vs placebo	Promising, awaits results
Rontalizumab	IFN α blocker	Phase II [18, 19]	159	Moderate to severe disease activity	BILAG	750 mg every 4 weeks (part 1), 300 mg every 2 weeks (part 2)	No general superiority; in low IFN signature it had significant superiority	No trials ongoing	-	-	-	Dubious results
Sifalimumab	IFN α blocker	Phase IIb [20]	431	SLEDAI-2K ≥ 6	SRI-4	200, 600, or 1200 mg every 28 days	Better SRI-4 response in high IFN signature group	No trials ongoing	-	-	-	Promising but not pursued
Anifrolumab	IFN α blocker	Phase IIb [21]	305	SLEDAI-2K ≥ 6	Composite of SRI-4 and corticosteroids reduction	300 or 1000 mg every 4 weeks	Better SRI-4 response in high IFN signature group	Several phase III including LN and skin lesions	-	-	-	Very promising, awaits results
IFN-kinoid	Induction of anti-IFN α antibodies	I/II [22]	28	Mild-to-moderate	-	30, 60, 120, or 240 μ g	Dose-related response anti-IFN α . Higher C3 level	Phase II trial ongoing	SLEDAI-2K ≥ 6	BICLA response at week 36	-	Promising, awaits results
SM101	Autoimmune complexes blockade	Phase IIa [23]	51	SELENA-SLEDAI ≥ 6 LN was included	Safety, SRI-4 and BILAG	6 and 12 mg/kg every week	Better SRI-4 response	No trials ongoing	-	-	-	Promising, needs clinical studies
SM201	Autoimmune complexes blockade	Pre-clinical [24]	-	-	-	-	B-cell inhibition	No trials ongoing	-	-	-	Very early to know

APC: antigen presenting cells; BICLA: BILAG-based Combined Lupus Assessment; BTK: Bruton's tyrosine kinase; ITT: intention-to-treat; SRI: Systemic Lupus Erythematosus Responder Index.

improvement was also achieved using BICLA, BILAG 2004; CLASI; joint counts and other variables. Influenza and herpes zoster infections were the most frequent AE. Further studies are ongoing in active SLE patients, including in LN (NCT02547922).

IFN- α -kinoid (IFN-K) is another option in blocking IFN α . IFN-K is a vaccine composed of IFN α 2b coupled to a carrier protein. It acts by inducing antibody production against all IFN α subtypes. A phase I/II trial of 28 patients with mild-to-moderate SLE showed a dose-related anti-IFN α response and improvement of C3 levels [22]. A phase II trial is ongoing to elicit IFN signature reduction and efficacy in SLE (NCT02665364).

Blocking immune complexes

Fc γ receptors (Fc γ R) are transmembrane proteins that recognize the Fc region of IgG. The binding of immune complexes (ICs) and Fc γ R initiates intracellular signalling, which results in an autoimmune response. Most of the Fc γ R molecules act as activating receptors and only Fc γ RIIB is an inhibitory receptor. Both types of receptors are expressed on the same cells. Negative signalling by Fc γ RIIB is mainly important for the regulation of activated B cells. SLE patients have a lower expression of Fc γ RIIB.

SM101 is an extracellular version of the human Fc γ RIIB. It binds to IC in SLE and blocks the Fc γ -mediated signal. Fc γ RIIB was chosen as a therapeutic target because of its limited human polymorphism and lack of immunogenicity. In a 24-week phase IIa trial, 51 SLE patients were randomized to receive SM101 or placebo weekly for 4 weeks. The primary outcome was safety and the secondary outcomes included SLEDAI, BILAG, physician global assessment, global response and renal parameters. No serious AE were reported. The SRI-4 response was twice as high in the SM101 group and in LN results was even better [23]. The results seem promising but phase III trials are needed.

Rather than binding to IC, binding to the receptor itself can produce an inhibitory response. SM201 is an anti-Fc γ RIIB mAb, it binds to Fc γ RIIB but allows the binding between IC and the Fc γ RIIB. A pre-clinical study showed that SM201 had a synergic action with IC resulting in a better inhibition of B cells [24]. It also seems to be restricted to activated B cells, allowing a functional memory response. Clinical trials are needed to understand if it's a valid therapeutic.

A resume of ongoing trials relevant to the approaches discussed in this review are shown in Table 1.

Conclusions

Biologic treatment of lupus has seen many false dawns. The relative successes of belimumab, rituximab, and atacicept (not discussed here) have been counterbalanced by the failures of many others including abatacept, tabalumab, blisibimod, and epratuzumab. But a number of new approaches, including fully humanized anti-CD20, PEGylated anti-CD40L, IFN α inhibitors and rigerimod, offer new hope that before too long we

will have a range of biologic options to offer our SLE patients that matches the choices we have for our RA and PSA patients.

Other approaches, not discussed here, such as blocking the Janus kinase/signal transducers and activators of transcription-pathway, IL-6 and nuclear factor kappa-light-chain-enhancer of activated B cells might also prove of value.

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